Exhibit 5

The Laryngoscope
Lippincott Williams & Wilkins, Inc., Philadelphia

CLINICAL STATE OF THE ART REVIEW

Allergic Fungal Rhinosinusitis: Current Theories and Management Strategies

Bradley F. Marple, MD

The combination of nasal polyposis, crust formation, and sinus cultures yielding Aspergillus was first noted in 1976 by Safirstein,[1] who observed the clinical similarity that this constellation of findings shared with allergic bronchopulmonary *Aspergillosis* (ABPA). Eventually this disease came to be known as allergic fungal rhinosinusitis (AFS). As clinical evidence of AFS accumulated, controversy regarding its etiology, pathogenesis, natural history, and appropriate treatment naturally emerged. Despite past and current efforts, many of these controversies remain incompletely resolved, but continuing clinical study has illuminated some aspects of the disease and has led to an improved understanding of AFS and its treatment. Fungi associated with the development of AFS are ubiquitous and predominantly of the dematiaceous family. The eosinophilic host response to the presence of these fungi within the nose and paranasal sinuses gives rise to those clinical manifestations of the disease (nasal polyps, expansile mucocele formation, allergic fungal mucin, etc.). Exposure alone to these fungi, however, appears to be insufficient to initiate the disease. At the present time it is likely that initiation of the inflammatory cascade leading to AFS is a multifactorial event, requiring the simultaneous occurrence of such things as IgE-mediated sensitivity (atopy), specific T-cell HLA receptor expression, exposure to specific fungi, and aberration of local mucosal defense mechanisms. A variety of treatment plans for AFS have emerged, but the potential for recidivism remains well recognized, ranging from 10% to nearly 100%, suggesting the need for continued study of this disease and fueling present controversy. This article is intended to review current data and theories regarding the pathophysiology of AFS, as well as the role of various surgical and nonsurgical forms of therapy. *Key Words:* **Fungus, allergy, rhinosinusitis.**

***Laryngoscope*, 111:1006–1019, 2001**

INTRODUCTION

The combination of nasal polyposis, crust formation, and sinus cultures yielding Aspergillus was first noted in 1976 by Safirstein,[1] who observed the clinical similarity that this constellation of findings shared with allergic bronchopulmonary *Aspergillosis*. Anecdotal reports that followed further supported the existence of this clinical entity, and gave rise to descriptive nomenclature such as "allergic *Aspergillosis* of the paranasal sinuses,"[2] "allergic Aspergillus sinusitis,"[3] and "allergic fungal sinusitis" or "allergic fungal rhinosinusitis" (AFS).[4] As clinical evidence accumulated, a number of significant questions were raised concerning such matters as the identity of involved fungi, the role of IgE and cell-mediated inflammation, reasons for differing regional patterns of disease, and effective forms of treatment. Despite the past and current efforts, most of these questions remain incompletely answered and are open to some controversy. However, within the answers to these and future questions, lie the facts that will undoubtedly influence our understanding and eventual treatment of AFS.

Controversy: Infectious versus Allergic?

The mere presence of fungus within the paranasal sinuses has traditionally raised questions concerning its potential for tissue invasion. Early attempts to treat many cases of AFS were often influenced by the fear that fungi within the paranasal sinuses axiomatically indicated an early form of invasive fungal sinusitis.[5] As a result, extensive surgical debridement followed by the use of systemic antifungal agents was commonplace. Eventually this notion was challenged by the theory that AFS may represent an immunological response to presentation of a fungal antigen within a susceptible host. Clarification of this controversy became critical to ultimate treatment choices.[6] If AFS truly represented an immunologically mediated disease, then the use of systemic antifungal medications, such as amphotericin B or itraconazole, would provide little benefit and could result in unnecessary toxic side effects. On the other hand, corticosteroids, which may be appropriate for immunologically mediated disease, would be counterproductive if AFS represented a precursor to invasive fungal disease.

From the Departments of Otolaryngology, Dallas Veterans Administration Hospital and Parkland Memorial Hospital, Dallas, Texas, U.S.A.

Editor's Note: This Manuscript was accepted for publication March 5, 2001.

Send Correspondence to Bradley F. Marple, MD, Department of Otolaryngology-Head & Neck Surgery, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390-9035, U.S.A.

Manning and Holman[7] addressed this controversy in two separate studies. In the first, 8 patients with culture-positive Bipolaris AFS were prospectively compared with 10 control subjects with chronic rhinosinusitis. Both groups were evaluated with (1) radioallergosorbent (RAST) and enzyme-linked immunosorbent assay (ELISA) inhibition to Bipolaris-specific IgE and IgG antibodies, and (2) skin testing with Bipolaris antigen. All 8 patients with AFS had positive skin test reactions to Bipolaris antigen as well as positive RAST and ELISA inhibition to Bipolaris-specific IgE and IgG. Eight of the 10 control subjects demonstrated negative results to both skin and serological testing, thus implicating the importance of allergy to fungal antigens (both in vivo and in vitro) in the pathophysiology of AFS.

In a complimentary study,[7] sinus mucosal specimens from 14 patients with AFS were compared with those from 10 control subjects with chronic rhinosinusitis. Immunohistochemical analysis for eosinophilic mediators (major basic protein and eosinophilic-derived neurotoxin) and a neutrophil-derived mediator (neutrophil elastase) was done to assess the underlying nature of inflammation. Inflammatory mediators derived from eosinophils predominated over neutrophil-derived mediators ($P < .00001$) in the AFS group, whereas significant differences were not present within the control group. The relative predominance of eosinophil-derived inflammatory mediators, as compared with neutrophil-derived inflammatory mediators, further support the association between non-infectious (i.e., immunologically mediated) inflammation and AFS, and helps to differentiate this disease from other forms of chronic rhinosinusitis.

The concept of eosinophilic activation associated with AFS was further supported by Feger et al.,[8] who studied eosinophilic cationic protein levels (ECP) in the serum and mucin of patients with AFS. No differences in serum ECP were detected between patients with AFS and control subjects, but ECP levels were significantly higher in mucin recovered from patients with AFS as compared with control subjects ($P < .01$).

Studies such as those by Manning et al.[7] and Feger et al.[8] offer strong immunological and histological data to support the argument that AFS represents an immunologically mediated disorder rather than a point on the spectrum of infectious fungal disease.

Associated Fungi: The Role of Dematiaceous Fungi

Until recently, the technical difficulty posed by attempted fungal cultures resulted in low rates of fungal recovery from patients with AFS. This left early investigators with limited information, hindering efforts at appropriate fungal identification. Early reports, which implied that *Aspergillus* sp. was the primary causative fungus associated with AFS, were based largely on the morphological appearance of the fungal hyphae identified histologically, as well as the recognized clinical and immunological similarities shared between AFS and allergic bronchopulmonary aspergillosis (ABPA). This notion was further supported by early serological testing, published by Katzenstein, demonstrating elevated specific IgE to *Aspergillus flavus* in two patients with AFS.[3] As the availability of culture-specific AFS information increased, however, it became apparent that many fungal species could be associated with development of the disease.[9]

In a 1996 review of the English literature performed by Manning, 263 cases of AFS were identified, of which 168 cases yielded positive fungal cultures. Of those 168 positive cultures, 87% were dematiaceous genera whereas only 13% yielded *Aspergillus*.[10] The dematiaceous family of fungi is one of several specific groups of fungi recognized for its pathogenic potential. Although not typically associated with invasive forms of fungal disease, dematiaceous fungi are recognized for the role they play in inhalant allergy. Specific genera within the dematiaceous family include *Bipolaris, Curvularia, Exserohilum. Alternaria, Drechslera, Helminthosporium,* and *Fusarium.*

PATHOPHYSIOLOGY

The exact pathophysiology of AFS remains a matter of conjecture for which several theories have been offered. One popular theory proposed by Manning and colleagues[11] is based on the assumption that AFS exists as the nasal correlate of allergic bronchopulmonary aspergillosis, and suggests that several interrelated factors and events lead to the development and perpetuation of the disease. First, an atopic host is exposed to fungi through normal nasal respiration, thus providing an initial antigenic stimulus. Gel and Coombs type I (IgE) and III (immune complex) -mediated reactions then trigger an intense eosinophilic inflammatory response. The resulting inflammation leads to obstruction of sinus ostia, which may be accentuated by anatomic factors such as septal deviation or turbinate hypertrophy, resulting in stasis within the sinuses. This, in turn, creates an ideal environment for further proliferation of the fungus, thus increasing the antigenic exposure. At some point this cycle becomes self-perpetuating and results in the eventual product of this process: allergic mucin, the material that fills the involved sinuses of patients with AFS. Accumulation of allergic mucin obstructs the involved sinuses and propagates the process.

While recent anecdotal and retrospective studies demonstrating the beneficial role of fungal immunotherapy in the treatment of AFS offer support to the theory proposed by Manning, many questions remain unanswered. If AFS represents an IgE-mediated disease, then why does it predominately occur in a unilateral fashion? Why does fungal-specific IgE remain elevated after prolonged fungal immunotherapy when normally it would be expected to decrease? Why do we fail to see the eventual rise in specific IgG levels resulting from development of IgG-blocking antibodies in response to fungal immunotherapy? These questions, and others, suggest that IgE-mediated inflammation may only contribute to the overall inflammatory cascade responsible for the ultimate development of AFS.

An alternative to this theory has been proposed by Ponikau et al.,[12] who have demonstrated the ubiquitous presence of fungi within the nose and paranasal sinuses through the use of an extremely sensitive fungal culture technique. Their report from the Mayo Clinic revealed the

presence of fungi in 94 of 101 (93%) patients undergoing surgery for any form of chronic rhinosinusitis. Of note, the presence of fungi was also identified within 100% of the control subjects used for comparison. Further evaluation of these patients revealed fungal-specific allergy to be uncommon. These findings have led to their belief that IgE-mediated inflammation is not crucial to the development of AFS, and that eosinophilic chemotaxis and activation may result from a T lymphocyte-mediated inflammatory cascade.

As with the theory proposed by Manning et al., many questions still exist with respect to the validity of the Mayo theories. If fungi are indeed ubiquitous and present within 100% of normal noses, then what separates those patients who develop AFS from the normal population? How do we account for the significant clinical difference between those patients included in the Mayo study (chronic rhinosinusitis) and those who satisfy more traditional diagnostic criteria of AFS? Are the fungal screening methods used so sensitive that normal fungal colonization is being mistaken for AFS, or does chronic rhinosinusitis merely represent an early form of clinically recognizable AFS?

As the clinical picture of AFS becomes increasingly apparent, its underlying pathophysiology remains steeped in controversy. Although it appears clear that the eosinophil plays an important role in the development of both AFS and some forms of chronic rhinosinusitis, the factors that ultimately trigger eosinophilic inflammation remain in question. Indeed, eosinophilic inflammation may occur as a final common pathway in response to a number of different inflammatory starting points. At the present time it is likely that initiation of the inflammatory cascade leading to AFS is a multifactorial event, requiring such things as IgE-mediated sensitivity (atopy), specific T-cell HLA receptor expression, exposure to specific fungi, and aberration of local mucosal defense mechanisms (Fig. 1).

EPIDEMIOLOGY

Allergic fungal rhinosinusitis is generally recognized as a disease distinct from other fungal forms of sinusitis. Most common among adolescents and young adults (mean age at diagnosis 21.9 y),[7] it is invariably associated with nasal polyposis and the presence of allergic fungal mucin. It is estimated that approximately 5% to 10% of those patients with chronic rhinosinusitis actually carries a diagnosis of AFS.[13–15] Atopy is characteristic of the disease: roughly two thirds of patients report a history of allergic rhinitis and 90% show elevated specific IgE to one or more fungal antigens. Approximately 50% of the patients in a series by Manning et al. had asthma. No linkage to aspirin sensitivity has been established.[7]

The incidence of AFS appears to be impacted by geographic factors. Review of the world's literature reveals the majority of sites reporting cases of AFS to be located in temperate regions with relatively high humidity.[6,15] Ferguson et al.[16] performed a questionnaire-based study within the United States to assess variations in the regional incidence of AFS. Results of this study indicated that the incidence of AFS varied remarkably based on the location of reporting sites and was most commonly encountered within the Mississippi basin, the southeast, and the southwest. The reason for this geographic difference remains unexplained.

CLINICAL PRESENTATION

History and Physical

Occasionally, the presentation of AFS may be dramatic, giving rise to acute visual loss,[17] gross facial dysmorphia,[11,18] or complete nasal obstruction. Patients may alternatively present with extensive nasal polyposis, chronic sinusitis (unilateral at first but often becoming bilateral), or recalcitrant disease, often recurring despite several surgeries. More often the presentation of AFS is

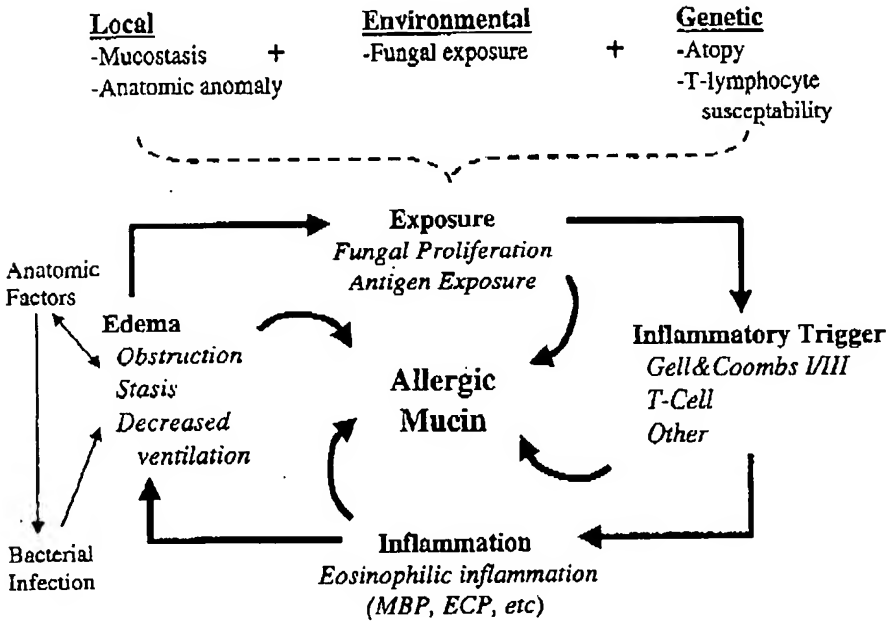

Fig. 1. AFS: a combination of predisposing factors—Multiple predisposing factors that occur simultaneously are most likely necessary to initiate the cyclic inflammatory cascade responsible for AFS.

subtle. Patients typically have gradual nasal airway obstruction and production of semisolid nasal crusts that, on inquiry, match the gross description of allergic fungal mucin. The development of nasal airway obstruction may have been so gradual that the patient is unaware of its presence. Likewise, if facial dysmorphia is present, its progression is often so slow that its identification escapes the patient and family members. Pain is uncommon among patients with AFS and suggests the concomitant presence of a bacterial rhinosinusitis.[10,20]

Patients with AFS are atopic but generally have been unresponsive to antihistamines, intranasal corticosteroids, and prior immunotherapy. The use of systemic corticosteroids may produce some relief of symptoms, but relapse typical follows completion of therapy. In contrast to patients who have invasive fungal sinusitis, patients with AFS are by definition immunocompetent.[20]

The range of physical findings on examination is typically broad, ranging from nasal airway obstruction resulting from intranasal inflammation and polyposis to gross facial disfigurement and orbital or ocular abnormalities. The slow accumulation of allergic fungal mucin imparts unique and predictable characteristics to the disease. Allergic fungal mucin is sequestered within involved paranasal sinus cavities. As its quantity increases, the involved paranasal sinus begins to resemble and behave in a way consistent with a mucocele (sometimes referred to as a fungal mucocele).[17] With time, bony remodeling and decalcification may occur, causing the disease to mimic "invasion" into adjacent anatomic spaces (Fig. 2). The location of bone destruction seems to be determined simply by the location of the disease, and this destruction often gives rise to exophthalmus, facial dysmorphia, or intracranial extension without tissue invasion.[21]

At times the extension of AFS into adjacent anatomic spaces can produce a dramatic clinical presentation. Highlighting the ocular manifestations of AFS, Carter et al.[22] reported six affected patients who presented with objective unilateral proptosis. This led them to report proptosis as the most common ophthalmologic manifestation of AFS. In a study by Marple et al.,[17] 82 patients with AFS were reviewed for specific ophthalmologic complications. Orbital involvement without visual loss was found in 14.6% of the patients and most commonly resulted in proptosis (encountered in 6.1% of patients) and telecanthus (7.3%). Visual loss from AFS, encountered in 3.7% of the patients in this series, was reversible with immediate surgical treatment of the underlying disease.

Radiological Findings

The accumulation of allergic fungal mucin eventually leads to the increasingly well-recognized radiographic findings characteristic of AFS. A recent study of sinus computed tomography (CT) scans from 45 patients with AFS objectively supports several previous clinical observations.[23] AFS, although bilateral in 51% of the cases reviewed, caused asymmetric involvement of the paranasal sinuses in 78% of the cases. Bone erosion and extension of disease into adjacent anatomic areas was encountered in 20% of the patients and was more likely to occur in the presence of bilateral, advanced disease. No difference was detected in the incidence of intracranial and orbital extension. Expansion, remodeling, or thinning of involved sinus walls was common (and was thought to be the result of the expansile nature of the accumulating mucin). Areas of high attenuation were found within the expanded paranasal sinuses in all patients. The authors point out that the CT specificity of diagnosing AFS could not be inferred from these findings because of the retrospective design of the study. Rare osteoid/chondroid matrix-producing sinonasal sarcomas or meningiomas can cause similar radiographic findings.

To further characterize patterns of bone erosion associated with AFS, Nussenbaum et al.[21] reviewed CT scans of 142 patients treated for AFS at a single institution. As seen in prior studies, bone erosion was encountered in approximately 20% of the patients studied. A statistically significant association was identified between expansion of paranasal sinuses involved with disease and the presence of bone erosion. The ethmoid sinus was the most commonly involved sinus, whereas the adjacent lamina papyracea was the most common bone to exhibit demineralization. Extension of AFS beyond the confines of the paranasal sinuses most commonly occurred into the orbit, followed by the anterior, middle, and posterior cranial fossae, respectively. Despite the sometimes-remarkable extension into adjacent anatomic spaces, no cases of histological invasion were identified.

Heterogeneous areas of signal intensity within paranasal sinuses filled with allergic fungal mucin are frequently identified on CT scans (Fig. 3). Although these findings are not specific for AFS, they remain relatively

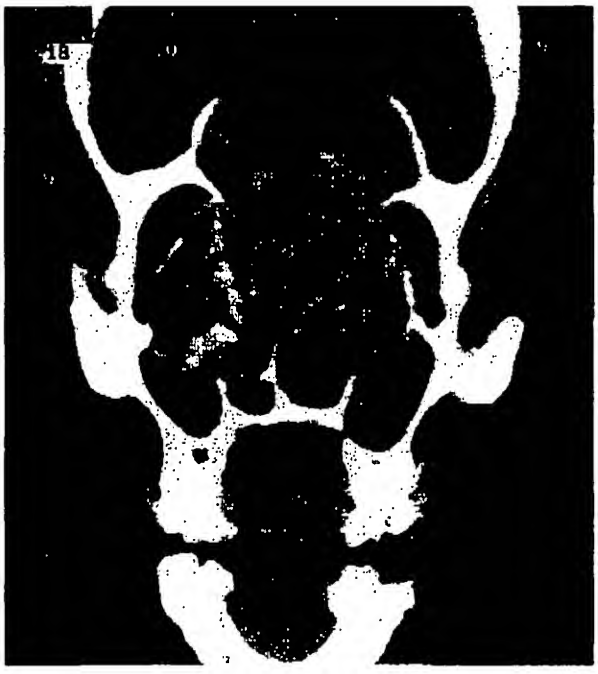

Fig. 2. Coronal CT demonstrates expansion of allergic fungal sinusitis into the orbits and anterior cranial fossa. Despite the massive encroachment noted on this CT scan, no fungal invasion of tissue was present.

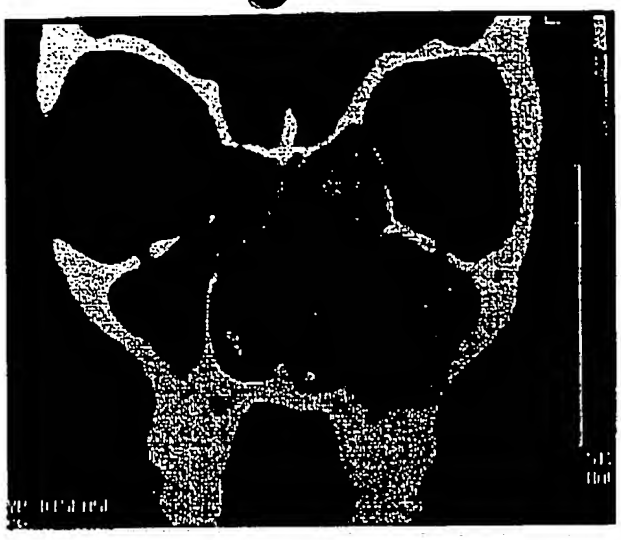

Fig. 3. Coronal CT scan demonstrating areas of signal heterogeneity within sinuses filled with allergic fungal mucin.

characteristic of the disease and may provide preoperative information supportive of a diagnosis of AFS. This characteristic, which is best identified using soft tissue algorithms on CT, has been the focus of some interest. An initial theory proposed the role of hemosiderin occurring within inspissated mucin as responsible for the areas of increased signal intensity. This was disputed by Zinreich et al.,[24] who was unable to identify increased hemosiderin within typical allergic fungal mucin.[23] Current evidence points to the presence of accumulations of heavy metals (e.g., iron and manganese) and calcium salt precipitation within inspissated allergic fungal mucin[23] as the most likely cause of these radiographic findings.

Magnetic resonance imaging (MRI) can also provide information useful in preoperative identification of allergic fungal mucin. Protein concentrations exceeding 28% result in a decreased T_1- and T_2-weighted MR signal intensity resulting from protein cross-linking and slower macromolecular motion.[25] This effect is more pronounced on T2-weighted images as a result of prolonged magnetic field relaxation times. The high protein and low water concentration of allergic fungal mucin, coupled with the high water content within surrounding edematous paranasal sinus mucosa, gives rise to specific MR characteristics (Fig. 4). Manning et al.,[26] in a series of 10 cases of AFS, demonstrated that hypointense central T1 signal, central T2 signal void, and the presence of increased peripheral T1/T2 enhancement was highly specific for AFS as compared with other forms of fungal sinusitis (invasive fungal sinusitis and fungal ball) and mucocele. The combined CT and MRI findings provided a radiographic appearance that was highly specific for AFS.[26]

Laboratory Findings

Immunological testing. The total IgE level has served as a useful tool to follow the clinical activity of allergic bronchopulmonary aspergillosis. Based on similar IgE behavior associated with recurrence of AFS, total IgE levels have been proposed as a useful indicator of AFS clinical activity. Total IgE values are generally elevated in AFS, often to more than 1000 U/mL.[3,27,28]

Patients with AFS generally demonstrate positive skin test and in vitro (RAST) responses for both to fungal and nonfungal antigens. Manning et al. first demonstrated the sensitivity of RAST,[29] who compared 16 patients with histologically confirmed AFS with a control group with chronic rhinosinusitis. Levels of fungal-specific IgE were uniformly elevated in all patients with AFS and corresponded with the results of fungal cultures. In contrast, levels of fungal-specific IgE were not elevated within the control group of patients with chronic rhinosinusitis. Moreover, patients with AFS appear to demonstrate a broad sensitivity to a number of fungal and nonfungal antigens. Mabry et al. have reported their experience, which indicates that patients with AFS are allergic to multiple fungal antigens, as well as many typical nonfungal antigens.[30]

Preliminary information suggests that methods of quantitative skin testing (in vivo) may provide even greater sensitivity than RAST[31] in patients with AFS. RAST has traditionally been considered less sensitive than skin testing during the investigation of atopy involving fungi. This has been attributed to technical problems such as difficulty in binding the mold antigen to a carrier

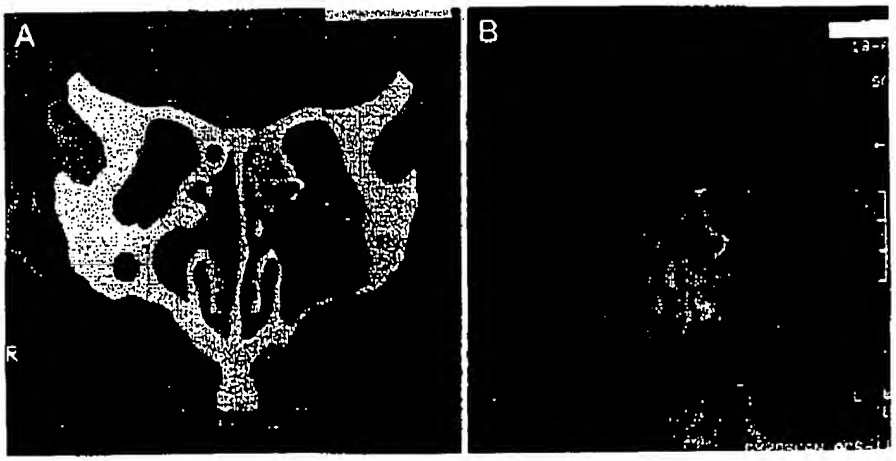

Fig. 4. Comparison of (A) CT scan and (B) T_1-weighted MRI of the same patient with allergic fungal sinusitis. Note that MRI (right) results in a decrease of signal intensity within the involved paranasal sinuses filled with allergic fungal mucin. (Reprinted with permission from Manning et al.[26])

substrate. To study the validity of this concept, Mabry et al.[31] prospectively evaluated 10 patients with AFS for sensitivity to 11 pertinent fungi by both RAST and dilutional intradermal testing. A predictable correlation between RAST and skin test scores was observed in many, but not all, cases. Most often, this disparity was in the form of greater sensitivity indicated by skin testing than by RAST, sometimes differing by as many as three classes. The lack of concordance was not confined to testing for fungi cultured from the sinuses, nor was it more or less pronounced in the case of dematiaceous fungi. The most likely causes for the disparity were thought to involve subtle differences in antigens used in skin test material as compared with RAST standards. Additionally, skin testing allowed for observation of delayed and late-phase reactions, a measure not possible by specific IgE testing with RAST. This study appears to emphasize the importance of both skin testing and specific IgE testing through RAST in the evaluation of patients with suspected AFS.

Gell and Coombs type I hypersensitivity in patients with AFS can be demonstrated by both elevation of serum total and fungal-specific IgE,[28,29] as well as by positive skin test results for both fungal and nonfungal antigens. This reaction does not, however, appear to be fungal-specific. Both in vitro (RAST) and in vivo methods (skin testing) have indicated sensitivity to numerous fungi, although generally only a single fungus is isolated by culture of corresponding allergic fungal mucin. This has been previously thought to represent either a common fungal epitope or a genetic predisposition toward fungal allergy in AFS. Recent work by Chrzanowski et al.[32] identified the presence of an 18-kD protein in allergic mucin obtained from patients with AFRS, which may represent such a "pan-antigen."

Histology of Allergic Fungal Mucin

It is the production of allergic mucin as defined by its clinical, histological, and radiographic characteristics that is unique to AFS and serves as a hallmark of the disease. Grossly, allergic fungal mucin is thick, tenacious, and highly viscous in consistency; its color may vary from light tan to brown or dark green.[13,19] This characteristic gross appearance has led to the use of such descriptive terms as "peanut butter" and "axle grease." Allergic fungal mucin is normally first encountered at the time of surgery; therefore, recognition of its presence is the initial step in establishing an accurate diagnosis of AFS. It is important to realize that it is the mucin, rather than paranasal sinus mucosa, that will provide the histological information necessary to make the diagnosis AFS.[33,34] Examination of mucosa and polyps obtained from involved paranasal sinuses reveal findings consistent with the inflammation of a chronic inflammatory process and should be done to establish that no fungal invasion is present.[34] Once mucin is collected, both culture and pathological examination is undertaken.

Initially described by Millar,[35] Lamb,[2] and Katzenstein,[3] histological examination of allergic mucin reveals a constellation of characteristic findings. Branching noninvasive fungal hyphae are identified within sheets of eosinophils and Charcot-Leyden crystals. Complete appreciation of all components of the mucin, however, is dependent on appropriate histological staining techniques. Hematoxylin and eosin (H&E) staining accentuates the mucin and cellular components of allergic fungal mucin. Using this stain, background mucin will often take on a chondroid appearance, whereas eosinophils and Charcot-Leyden crystals are heavily stained and become easily detected. Fungi fail to stain with H&E, however, and may be implicated only by their resulting negative image against an otherwise stained background. Given that fungal hyphae are frequently rare, scattered, and fragmented within allergic mucin, identification is extremely difficult unless specific histological stains are used. Fungal elements are recognized for their unique ability to absorb silver. This property is the basis for various silver stains, such as Grocott's or Gomori's Metamine silver (GMS) stain, which turn fungi black or dark brown (Fig. 5). The use of a fungal stain complements the findings of initial H&E stain and is extremely important in the identification of fungi.

Culture of Fungi

Fungal cultures of allergic fungal mucin may provide some supportive evidence helpful in the diagnosis and subsequent treatment of AFS, but must be interpreted with caution. It is important to realize that the diagnosis of AFS is not established or eliminated based on the results of these cultures. The variable yield of fungal cultures (64%–100%[10]) renders AFS in the presence of a negative fungal culture possible. Conversely, a positive fungal culture fails to confirm the diagnosis of AFS, because it may merely represent the presence of saprophytic fungal growth. It is for this reason that the histological appearance of allergic mucin remains the most reliable indicator of AFS.

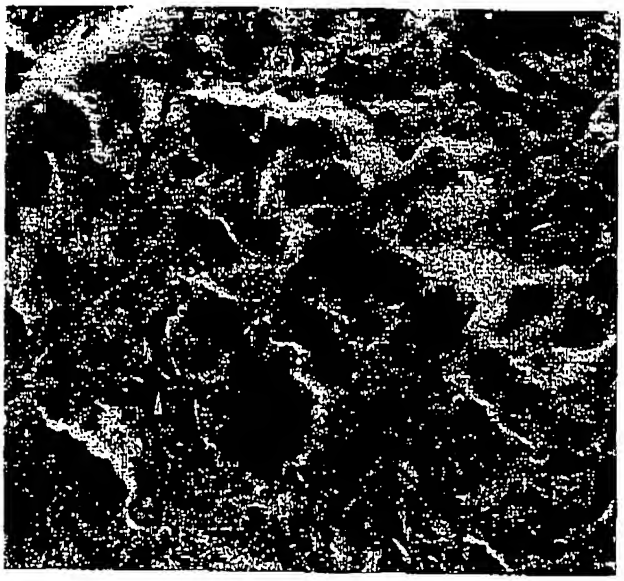

Fig. 5. Gomori's Metamine silver (GMS) stain of allergic mucin reveals a darkly stained fungal hyphae (arrow) within a cellular background.

DIAGNOSTIC CRITERIA

Given that nasal polyposis is not unique to AFS, and that fungi may be present within the nose and paranasal sinuses in multiple diseases, AFS must be differentiated from other mycotic diseases of the sinuses. Other recognized sinonasal processes that must be differentiated from AFS include saprophytic fungal growth in an otherwise normal nose,[38] fungal ball (formerly referred to as mycetoma),[39] eosinophilic mucin sinusitis,[40,44] and invasive fungal sinusitis.

At the current time, consensus is lacking concerning diagnostic criteria for AFS, although several sets of criteria have been proposed. Allphin and colleagues[38] thought the combination of opacified paranasal sinuses on radiography, characteristic histological findings of allergic mucin, and laboratory evidence of allergy was sufficient to differentiate AFS from other forms of rhinosinusitis. Lowery and Schaefer[37] proposed a more specific set of diagnostic criteria, which included eosinophilia, immediate skin reactivity or serum IgE antibodies to fungal antigen, elevated total IgE level, nasal mucosal edema or polyposis, histopathologic findings of allergic mucin containing noninvasive fungal hyphae, and characteristic CT or MRI findings.

Based on the analysis of 15 cases of AFRS, Bent and Kuhn[14] demonstrated five common characteristics: Gell and Coombs type I (IgE-mediated) hypersensitivity, nasal polyposis, characteristic radiographic findings, eosinophilic mucin without fungal invasion into sinus tissue, and positive fungal stain of sinus contents removed at the time of surgery (Table I).

TREATMENT

Based on a postulated schema of the pathophysiology of AFS, a variety of treatment plans addressing its multiple contributing factors have emerged. Medical control of the disease has made use of various combinations of antifungal medications, corticosteroids, and immunotherapy with varying degrees of disease control. Attempts to control this disease by only partially addressing the underlying causes has likely contributed to a high rate of recidivism. Successful treatment of AFS requires that the treatment plan account for each factor responsible for the propagation of the disease. The "AFS cycle," as described earlier, suggests that atopy, continuous antigenic exposure, and inflammation all play key roles in the perpetuation of the disease. In theory, individually accounting for each of these factors will provide for the best chance of long-term disease control.[19] This comprehensive approach to management depends on complete removal of all fungal mucin (usually requiring surgery), and long-term prevention of recurrence through either immunomodulation (immunotherapy and/or corticosteroids) or fungistatic antimicrobials (Figs. 6 and 7).

TABLE I.
Bent and Kuhn Criteria for AFS.[14]

Type I hypersensitivity (history, skin test, or serology)
Nasal polyposis
Characteristic radiographic findings
Eosinophilic mucus demonstrating fungus without tissue invasion

AFS = allergic fungal rhinosinusitis.

Traditional Surgical Therapy

The single invariable component of combination therapy remains surgical removal of the inciting fungal allergic mucin and marsupialization of the involved sinuses. For this reason, surgery has played an important role in the management of AFS since its earliest reports. An aggressive surgical posture was initially adopted resulting from a perceived risk of fungal invasion. In 1979, reporting their experience of four patients with "paranasal aspergillosis," McGuirt et al.[41] stated "without question, the treatment of paranasal sinus aspergillosis is surgical—the key to successful surgical treatment is the removal of diseased mucosa and aeration and drainage of the involved sinus." [41(p. 1567)] This was frequently accomplished through the use of open antrostomies with radical removal of mucosa, intranasal sphenoethmoidectomies, and Lynch frontoethmoidectomies. Despite such aggressive therapy, recidivism remained high and most patients required multiple surgical procedures.[42,49]

The clinical appearance of the disease often confused the underlying diagnosis, further influencing surgeons to adopt a more radical stance. Radiographic evidence of "invasion" into adjacent spaces, such as the orbit or intracranial cavity, was frequently interpreted as evidence of malignancy or invasive fungal disease. It logically followed that surgical approaches appropriate for these serious conditions, such as lateral rhinotomy, facial-degloving approaches, and craniofacial resection, would be performed. Sarti,[49] in 1988, reported a case of "paranasal aspergillosis" with extension into the anterior cranial fossa and sella turcica. Although no histological invasion of mucosa was demonstrated, the presence of fungal hyphae coupled with dramatic radiographic bony erosion yielded a diagnosis of "invasive aspergillosis." The patient

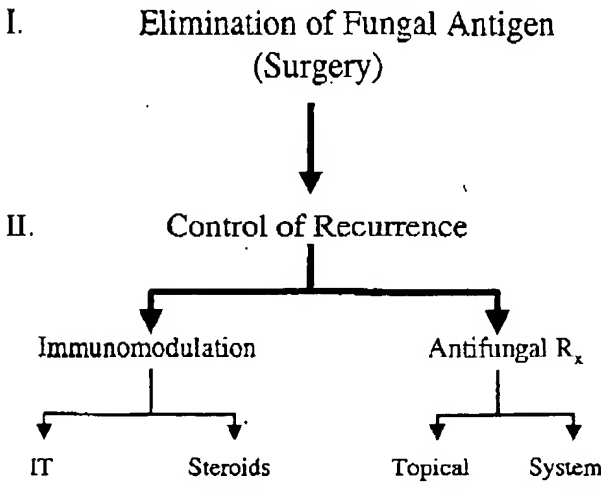

Fig. 6. Treatment principles: Long-term control of allergic fungal sinusitis requires both elimination of fungal antigen and control of its recurrence.

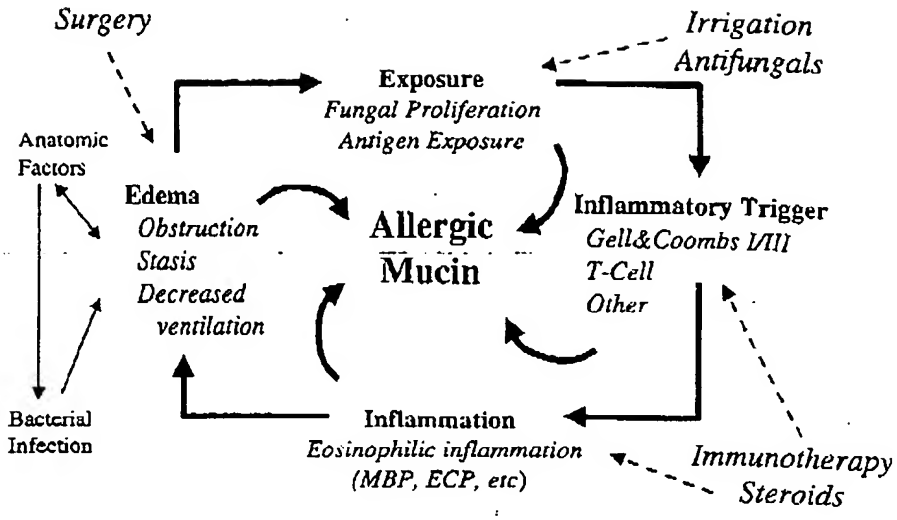

Fig. 7. Rationale for various therapeutic interventions.

unfortunately died as a result of a pulmonary embolus following a craniofacial resection.

Increased acceptance of specific immunological hypersensitivity as the cause for AFS has led to changes in its management. These changes have involved both the medical and surgical arms of therapy. While systemic use of antifungal medications has largely been replaced by immunomodulation, radical surgery for AFS has given way to more conservative, tissue-sparing approaches. Mabry et al.[30] refer to this surgery as "conservative, but complete," relying almost completely on endoscopic techniques.

Surgical Implication of the Physical Characteristics of AFS

The slow accumulation of allergic fungal mucin over an extended period of time within involved paranasal sinuses imparts unique and predictable characteristics to the disease. As the quantity of mucin increases, the involved paranasal sinus begins to resemble a mucocele (sometimes referred to as a fungal mucocele). With time, bony remodeling and decalcification may occur, causing the disease to mimic "invasion" into adjacent anatomic spaces.[43–45] The location of bone demineralization and extension appears to be determined by the location of the expansile disease and is thought to occur as a result of a combination of pressure and local inflammatory mediators. This process may give rise to exophthalmos, facial dysmorphia, and intracranial extension.[45]

It is the physical characteristics of AFS that influence its surgical treatment. By the very nature of the disease, AFS creates a series of local inflammatory responses, each capable of producing polyposis and allergic mucin. The clinical and radiographic involvement can be extensive at times, causing large-scale bone dissolution and encroachment into adjacent anatomic spaces. These typical features of AFS, once used to justify radical surgical approaches, can actually aid in the pursuance of a more conservative surgical approach.[46]

Nasal polyposis is inherent to AFS[47] and can range from subtle to extensive, causing distortion of local anatomy and loss of useful surgical landmarks. Bleeding often occurs in response to surgical manipulation of the polyps, increasing the potential for disorientation. The operating surgeon must recognize that these factors, in combination with the high likelihood of bony dehiscence, increase the risk of iatrogenic injury.

Aside from these problems, polyps can provide an important intraoperative role by serving as a marker of disease. AFS causes a relatively consistent configuration of disease. The involved paranasal sinus, acting as a reservoir for allergic fungal mucin, is the epicenter of the disease process. Allergic fungal mucin completely occupies the sinus cavity, whereas the lining mucosa, demonstrating only mild to moderate inflammation, remains an intact barrier to the fungus.[19,34] More significant inflammation located at the sinus ostia gives rise to polyps that extend into the infundibulum, middle meatus, sphenoethmoid recess, and nasal cavity. Recognition of this allows the surgeon to "follow the polyps to the disease."[46]

The resulting nasal polyposis can also facilitate the surgical treatment of AFS in another fashion. The expansile behavior of AFS increases access to involved paranasal sinuses. As revealed radiographically, the combination of slowly growing nasal polyps and accumulating allergic fungal mucin expand the involved paranasal sinuses as well as the surgical route to the involved sinuses. Enlargement of the nasal cavity, middle meatus, and frontal recess provide the surgeon with access adequate to deal with the disease in even the most difficult areas, such as the frontal sinus.[13]

After surgical access to the involved sinus is achieved, a dilated cavity filled with allergic fungal mucin is encountered. Because of its noninvasive behavior, the allergic mucin may be removed in a blunt fashion, leaving the involved sinus completely lined with intact mucosa. Preservation of mucosa provides protection of adjacent anatomic structures, even in the face of large areas of bony dehiscence.

Surgical Technique

To minimize recurrence of disease, treatment of AFS is directed at removal of the inciting antigenic material

through complete surgical removal of allergic mucin and debris, while also ameliorating the underlying inflammatory process through the use of limited systemic and topical steroid preparations. One accepted preoperative medical regimen is to initiate systemic corticosteroid therapy (0.5–1.0 mg/kg prednisone per day) approximately 1 week before surgery to decrease intranasal inflammation and nasal polyp volume. Additionally, preoperative antibiotics are instituted as a result of the frequency of concomitant postobstructive bacterial rhinosinusitis.[19]

At surgery, three goals should be achieved. First, surgery should result in complete extirpation of all allergic mucin and fungal debris, thus greatly reducing or eliminating the antigenic-inciting factor within the atopic individual. At times this may be challenging. Access to the frontal sinus and other potentially involved spaces, such as extramural ethmoid cells, or a pneumatized pterygoid of the sphenoid, may be limited. However, as noted previously, the expansile behavior of the disease tends to widen natural tracts into these normally limited areas, facilitating surgical manipulation.

The next goal of surgery is to produce permanent drainage and ventilation of the affected sinuses while preserving the integrity of the underlying mucosa. This has been greatly aided by the recent advent of tissue-sparing instrumentation.[48] Even in the setting of significant dissolution of the ethmoid roof, lamina papyracea, clivus, and sphenoid planum, wide marsupialization of diseased areas can be achieved without causing trauma to the underlying mucosa. Careful preservation of mucosa ensures that underlying periosteum, dura, and/or periorbita remain free of penetrating injury. Sinonasal polyposis may initially preclude orientation, but removal in a controlled fashion using powered microdissection provides the operating surgeon with eventual access to areas of fungal presence. After adequate ventilation and drainage are achieved, the preserved underlying mucosa is able to revert to its normal state.

Adequate ventilation and drainage also provide for the final goal of surgery: postoperative access to the previously diseased areas. Even under ideal conditions, small residua of fungus may remain in situ, inciting recurrence if not controlled postoperatively. Surgery should be performed with facilitation of postsurgical care in mind. This goal can be reliably attained in most cases while preserving the integrity of important intranasal structures, such as the middle and inferior turbinates.

These surgical goals can be accomplished through a number of approaches and techniques, the choice of which will ultimately be influenced by the experience and training of the surgeon. Endoscopic-powered instrumentation has demonstrated its effectiveness through the ability of this technique to remove soft tissue and thin bone while maintaining superb visibility. Great care should be exercised when using powered instrumentation, however, as the well-recognized bone dissolution associated with AFS increases the potential risk of inadvertent orbital and/or intracranial penetration. In the event of extensive remodeling or bone erosion, image-guided systems may be of benefit.[46]

Postoperative care begins immediately after surgery in the form of nasal saline irrigation. Weekly clinic visits are initially required to allow regular inspection of the operative site and debridement of crusts and retained fungal debris. Systemic corticosteroids, which were initiated before surgery, are continued during the postoperative period and slowly tapered during the process of healing. The length of corticosteroid treatment is based on the discretion of the managing physician as well as the form of postoperative adjunctive medical management used to further control the disease. The period of postoperative corticosteroid coverage may be used to initiate other forms of medical management.

Complications of Surgery

In the majority of cases, surgery is performed without incident, but the pathological behavior of AFS theoretically increases surgical risk. Nasal polyposis, expansile accumulations of allergic mucin, as well as poor intraoperative hemostasis may increase spatial disorientation. Additionally, areas of bony dehiscence may confuse or distort anatomic boundaries while offering little protection to the orbit and intracranial cavities. On the other hand, a less than complete surgical procedure (in an attempt to decrease iatrogenic injury) is likely to lead to incomplete retrieval of allergic fungal mucin and rapid recurrence of AFS.

Based on currently available data regarding the behavior of AFS, there is little risk of fungal invasion in the immunocompetent host. It appears that rare exceptions may occur. Tsimakas et al.[49] report a single case of an Aspergillus frontal lobe abscess which occurred after surgical treatment of AFS which had expanded into the anterior cranial fossa. This case, however, may represent seeding of the intracranial cavity as a result of inadvertent dural penetration and emphasizes the importance of mucosal preservation.

In addition to fungal or bacterial seeding, surgical penetration beyond the limits of the paranasal sinuses may result in injury of structures within the orbit or intracranial cavity. Such transgressions can cause diplopia, blindness, hemorrhage, stroke, intracranial hemorrhage, and/or cerebrospinal fluid rhinorrhea. The patient shown in Figure 8 was referred to our clinic after surgery for AFS and illustrates this point. Violation of the left periorbita resulted in trauma and fibrosis of the ipsilateral medial rectus muscle causing subsequent permanent diplopia. Violation of the anterior cranial fossa dura resulted in development of an encephalocele. Avoidance of such an injury requires careful attention to anatomic orientation and strict preservation of mucosa and underlying tissues.[49]

Erosion by AFS of the osseous boundaries separating the intracranial fossa from the sinonasal cavities may increase the risk of subsequent encephalocele formation. It is commonly accepted within the otologic community that dural exposure in the absence of dural injury along the tegmen mastoideum rarely results in the development of an encephalocele.[50] Unfortunately, no analogous information within the rhinologic literature exists. It is logical to assume, however, that eventual encephalocele forma-

tion may occur as a result of a combination of factors, including dural injury, location of bony dehiscence, and/or size of the bony dehiscence. Monitoring for development of encephaloceles may be necessary in selected cases, because their occurrence may require subsequent repair of the bony dehiscence.[46]

MEDICAL THERAPY

Corticosteroids

The origin of corticosteroid therapy for the long-term management of AFS arose directly from the success of this strategy in the treatment of ABPA. The potent antiinflammatory and immunomodulatory effects of corticosteroids appear to be well suited to control recurrence of disease. This concept was emphasized by Bent et al.,[61] who noted eventual universal recurrence of AFS in their patients who were not treated with systemic corticosteroids. Schubert and Goetz[27] further studied the role of systemic corticosteroids in the postoperative management AFS, demonstrating a significant increase in the time to revision sinus surgery in those patients with AFS who received prolonged courses of postoperative corticosteroids. Postoperative corticosteroid therapy in this study ranged from 2 to 12 months, with improved outcomes recorded among those patients who were placed on longer courses of therapy. At the present time, however, the optimal dosing regimen and length of therapy remain unclear.

Topical corticosteroids are accepted as a standard therapy in the postoperative treatment of AFS, but they possess a limited benefit before surgery because nasal access is restricted. After surgery, however, they may be effective in controlling local inflammation.

Complications of corticosteroids. The well-recognized benefits of systemic corticosteroids are counterbalanced by numerous potential adverse effects, including growth retardation, diabetes mellitus, hypertension, psychotropic effects, gastrointestinal side effects, cataracts, glaucoma, osteoporosis, and aseptic necrosis of the femoral head. Schubert et al.[27] reported no adverse effects among their series of 67 patients with AFS treated for up to 1 year with systemic corticosteroids, but long-term follow-up for this form of therapy is lacking. The side effect profile of systemic corticosteroids warrants careful consideration when they are used in a long-term approach to control AFS.

Topical corticosteroids generally present fewer side effects than systemic corticosteroids, based on their limited bioavailability. Long-term use, especially when used at high dosages or in combination with inhaled corticosteroids, present a risk of hypothalamic-pituitary-adrenal axis suppression, cataract formation, growth retardation, nasal bleeding, and nasal septal perforation in rare cases. Like with any form of chronic therapy, patients using topical corticosteroid sprays should be closely monitored.

Immunotherapy

The similarity between AFS and ABPA led to an empiric (and theoretical) concern that immunotherapy using specific fungal antigens in patients with either of these diseases might incite further allergic reactions by adding

Fig. 8. Coronal CT scan of a patient after endoscopic surgery for allergic fungal sinusitis. Violation of mucosa and dura of the anterior cranial fossa resulted in encephalocele formation (double arrows), whereas violation of the contralateral periorbita produced trauma and fibrosis of the medical rectus muscle (single arrow).

to the patient's fungal antigenic stimulus.[62] This concern specifically addressed the possible exacerbation of immune complex development and deposition. However, in the case of AFS, surgery theoretically allows removal of the inciting fungal load from the paranasal sinuses. Based on this difference between AFS and ABPA, it has been postulated that immunotherapy after surgery may be beneficial, rather than harmful, as a component of treatment for AFS.[52,63]

To investigate the safety of fungal immunotherapy as an adjunct to AFS treatment, a prospective study was performed to examine the response of patients with AFS, following adequate surgery, to immunotherapy with all antigens (fungal and nonfungal) to which the patients were sensitive.[52] In the first year of this study, clinical status was not shown to worsen, the patients did not require systemic corticosteroids, most patients were able to discontinue topical corticosteroid therapy, and AFS recurrence was markedly diminished among those patients compliant with the regimen. Follow-up revealed similar findings at 2 and 3 years.[30,63] A complimentary study retrospectively compared 11 patients treated in this manner with 11 age- and disease-matched control subjects who received the same surgical and medical treatment but no immunotherapy. A statistically significant difference was noted between the two groups. The cohort receiving immunotherapy as part of their treatment performed better in both quality of life scores as well as objective endoscopic measures of mucosal edema.[64]

In a series of eight patients in whom immunotherapy was given for 3 to 5 years and then discontinued, no recurrences were seen up to 17 months after discontinuation.[55] Additional study is necessary, but initial work suggests that a role may exist for immunotherapy in the overall treatment strategy for AFS.

TABLE II.
Protocol for Immunotherapy in Allergic Fungal Sinusitis.

1. After successful surgical exenteration of sinuses and confirmation of diagnosis, allergy evaluation and testing (RAST or quantitative skin test) for typical panel of non-fungal antigens appropriate for the area. Test (RAST or quantitative skin test) for all relevant molds (fungi) available. Discuss treatment protocol with patient and obtain informed consent.
2. Instruct patient in avoidance measures for molds. Adjust pharmacotherapy as necessary.
3. Prepare vial of all positive non-fungal antigens and second vial of all positive fungal antigens. Perform vial test with each.
4. Administer immunotherapy weekly, with dosage advancement as tolerated, placing one injection from each vial in a different arm. This allows for accurate recognition of cause of any local reactions noted.
5. Observe patient regularly, adjust dosage as necessary if local reactions or adverse changes in nasal signs/symptoms occur. Patient should be examined regularly by endoscopy to watch for re-accumulation of allergic mucin or reformation of polyps, and cleaning, medical management, etc. carried out.

As dosage advancement permits (generally by second vial), may combine antigens into one vial and continue for a 3–5-year regimen as per standard practice.
RAST = radioallergosorbent inhibition test.

Technique of immunotherapy in AFS. In initial studies, only immunotherapy for positive fungal antigens was administered for the first 6 months to be certain that any effects (either positive or negative) on the disease process were the result of the administration of fungal antigens. Later, both fungal and nonfungal antigens to which the patient was found to be allergic were included in the treatment mix. However, it remains advisable to administer these in two separate vials for the first several months of treatment to more easily assess the source of any untoward local reaction and more efficiently advance treatment dosage. After maintenance levels are achieved, the fungal and nonfungal antigens may be combined into one vial (Table II).

A common misconception is that immunotherapy for *only* those fungi identified by culture from allergic fungal mucin should be included in the testing/treatment regimen for a patient. Because of the recognized inconsistency of current fungal culture techniques, a positive culture will not be obtained in all cases. Conversely, the presence of fungi on culture of sinus contents does not make the diagnosis of AFS. One successful approach has been to test for a wide variety of molds (the choice being dictated by experience gained in testing and treating allergy patients in the region) and to include all positive reactors in the treatment set[30] (Table III).

TABLE III.
Fungal Antigens in Current Testing and Treatment Protocol at the University of Texas Southwestern Medical Center at Dallas (in approximate relative order of local [Dallas, TX] importance).

- Helminthosporium
- Alternaria
- Stemphyllium
- Curvularia
- Aspergillus
- Epicoccum
- Fusarium
- Mucor
- Pullularia
- Cladosporium
- Penicillium

Reproduced from Mabry RL, Marple FB, Folker RJ, Mabry CS. Immunotherapy for allergic fungal sinusitis: 3 years' experience. *Otolaryngol Head Neck Surg* 1998;119:648–651.

Advancement and adjustment of dosage is carried out in the usual fashion.[56] Although late local reactions (induration greater than 30 mm in diameter occurring 24–48 h after an injection) are said to be more common when administering immunotherapy for molds than for other antigens, this has not been the reported experience in treating patients with AFS.[31] Systemic reactions to immunotherapy likewise have not been observed.

Based on experience, it is currently recommended that immunotherapy be administered to patients with AFS for the same duration as recommended for allergy patients in general: 3 to 5 years.[55]

Complications of immunotherapy. At the time of this publication, no treatment-related complications have been identified when immunotherapy follows appropriate surgical extirpation of all allergic mucin. This, however, should not promote a sense of false security concerning this form of therapy, as immunotherapy continues to represent a new and incompletely understood treatment modality. In general terms, immunotherapy may potentially lead to worsening of local or systemic disease, specifically if the patient continues to be exposed to a significant antigenic load.

Ferguson[40] reported seven patients who received immunotherapy for the treatment of AFS. The five patients who received immunotherapy before surgical removal of all allergic mucin either symptomatically worsened or failed to improve in response to therapy. In contrast to these findings, the two patients who underwent surgery before initiation of immunotherapy responded well to this treatment modality. This small study supports the concept that immunotherapy administered in the presence of an ongoing antigenic load (in this case fungus) raises the risk of untoward complications of therapy (immune complex deposition, delayed or late phase reactions, local reactions, etc.).

Another permutation of this concern occurs when AFS presents concomitantly with ABPA.[57] Unlike the situation of AFS, the fungi within the lower respiratory tract of those patients with ABPA cannot be surgically removed, thus resulting in a retained antigenic load. Moreover, while the clinical manifestations of AFS are sometimes dramatic, they are rarely life threatening. The threat of ABPA is potentially much greater. Given the lack of information regarding the effects of immunotherapy on ABPA, great care should be taken when immunotherapy is given in this situation.[58]

Antifungals

Systemic antifungal therapy for AFS was initially proposed to control the theoretical potential for progres-

sion to invasive forms of fungal sinusitis. As the unacceptably high rate of recidivism after surgery alone was recognized, antifungal therapy was often used in an attempt to provide some degree of control over recurrence of AFS. The early use of amphotericin B yielded to the use of less toxic agents, such as ketoconazole, itraconazole, and fluconazole, but the poor in vivo activity of these agents against dematiaceous fungi was soon discovered.[7] Objective data on the effects of this form of therapy for AFS have been limited. Denning et al.[59] studied the effect of systemic itraconazole in patients with ABPA and showed a decrease in both total IgE (used as a marker of disease severity) and systemic corticosteroid requirements. Anecdotal reports of systemic itraconazole to prevent AFS recurrence offer mixed results. Ferguson[60] points out that the expense, limited available data, and potential drug-related morbidity of systemic antifungal therapy may limit the usefulness of this form of treatment for noninvasive fungal disease.

Topical application of antifungal agents may hold some benefit in the control of postoperative recurrence, and studies of this form of treatment are currently underway. Bent and Kuhn[61] studied the in vitro susceptibility of fungi commonly encountered in patients with AFS and determined that minimal inhibitory concentrations can be exceeded with certain antifungal agents when applied topically. Similarly, Ponikau[12] supports the use of topical antifungal agents. Supportive data are pending.

Complications of antifungal therapy. Antifungal medications may cause potentially serious side effects, which warrant consideration when these preparations are used as a form of treatment for AFS. The well-known complications associated with amphotericin B include acute renal failure, anemia, agranulocytosis, acute liver failure, cardiopulmonary hypertension, and hemorrhagic gastroenteritis. Itraconazole and fluconazole offer a slightly safer form of antifungal therapy, but may still give rise to drug-induced cardiac dysrhythmias, hepatic dysfunction, urticaria, and anaphylaxis.[62]

Recurrence of Disease

The potential for AFS recidivism is well recognized and ranges from 10%[63] to nearly 100%.[60] Published rates of AFS recurrence, however, can be misleading and are highly dependent on length of follow-up. To emphasize the importance of long-term surveillance, Bent et al.[61] pointed out that in their experience the often-dramatic initial response to surgical therapy was eventually replaced by recurrence of AFS in the absence of ongoing therapy. Similarly, Kupferburg et al.[64] followed the appearance of sinonasal mucosa of 24 patients treated with combined medical and surgical therapy for AFS. Nineteen of the 24 eventually developed recurrence of disease after discontinuation of systemic corticosteroids, but they observed that endoscopic evidence of disease generally preceded return of subjective symptoms.

AFS recidivism appears to be influenced by long-term postoperative therapy. Schubert et al.[27] reported the long-term clinical outcome of 67 patients following initial surgical therapy for AFS. Patients treated with at least 2 months of oral corticosteroids were compared with those who received no corticosteroids. At 1 year after initial surgery, patients treated with oral corticosteroids were significantly less likely to have experienced recurrent AFS (35%) than those who had not (55%). It is important to realize, however, that AFS recidivism remains high despite appropriate postoperative medical therapy. As addressed earlier in this chapter, fungal- and nonfungal-specific immunotherapy holds some potential as a form of postoperative treatment in patients with AFS, but clinical failures can arise during immunotherapy. Marple et al.,[63] in a review of 42 patients who had received immunotherapy after surgery, reported 4 recurrences of disease, which were attributed to either noncompliance with immunotherapy or inadequate operative extirpation of allergic fungal mucin.

CONCLUSION

Allergic fungal sinusitis is a relatively newly characterized disease entity that commands a great deal of interest. Large amounts of information are being generated addressing the underlying etiology of the disease, its clinical presentation, and forms of treatment. Although controversy still exists, recent evidence supports the theory that AFS represents an immunological, rather than infectious, disease process. An improved understanding of this underlying disease process has led to an evolution in the treatment of AFS. Medical therapy has begun to shift from an emphasis on systemic antifungal therapy to various forms of topical treatment and immunomodulation. Likewise, surgical treatment of AFS, still a crucial component of the overall treatment plan of the patient, has shifted from radical to a more conservative, yet complete approach. Although important, surgery alone does not lead to a long-term disease-free state. A comprehensive management plan incorporating both medical and surgical care remains the most likely way to provide long-term disease control for AFS.

SUMMARY

1. AFS represents an immunologically mediated, rather than infectious, disease. Although the exact nature of the underlying inflammatory trigger is not yet known, atopy, fungal exposure, and possible T-lymphocyte stimulation appear to play a role in its development.
2. Local inflammation appears to be related to eosinophil chemotaxis and degranulation.
3. Fungal invasion of tissue is NOT associated with AFS. If this is encountered, then invasive fungal disease must be assumed.
4. Radiographic destruction and expansion of disease beyond the confines of the paranasal sinuses is not uncommon and is not associated with tissue invasion.
5. Total IgE levels can help to monitor the activity of the disease in some patients.
6. Diagnosis of AFS is not dependent on the culture of fungus from the nose or paranasal sinuses, but is established by the clinical manifestations of the

disease and histologic presence of allergic fungal mucin (in the absence of fungal invasion of tissue).

7. Care should be observed during the surgical treatment of AFS, due to the high incidence of local osseous dissolution and remodeling.
8. Surgical therapy in the absence of continued medical therapy is associated with a high rate of recidivism.
9. The role of various medical therapies is currently emerging. Ongoing studies will clarify the role of corticosteroids, antifungal medication, and immunotherapy in the treatment of AFS.
10. Despite the form of therapy chosen for the patient with AFS, long-term follow-up is essential.

Acknowledgments

The author thanks Richard L. Mabry, MD, for his editorial help and guidance and Frances Yates for her invaluable help in the preparation of the manuscript.

BIBLIOGRAPHY

1. Safirstein B. Allergic bronchopulmonary aspergillosis with obstruction of the upper respiratory tract. *Chest* 1976;70: 788–790.
2. Lamb D, Millar J, Johnston A. Allergic aspergillosis of the paranasal sinuses. *J Pathol* 1982;137:56.
3. Katzenstin A, Greenberger P, Sale S. Allergic aspergillus sinusitis: a newly recognized form of sinusitis. *J Allergy Clin Immunol* 1983;72:89–93.
4. Robson J, Hogan P, Benn R, et al. Allergic fungal sinusitis presenting as a paranasal sinus tumor. *Aust N Z J Med* 1989;19:351–353.
5. Gungor A, Adusmilli V, Corey JP. Fungal sinusitis: progression of disease in immunosuppression—a case report. *Ear Nose Throat J* 1998;77:207–215.
6. Corey J, Delsupehe K, Ferguson B. Allergic fungal sinusitis: allergic, infectious or both? *Otolaryngol Head Neck Surg* 1995;110–119.
7. Manning SC, Holman M. Further evidence for allergic fungal sinusitis. *Laryngoscope* 1998;108:1485–1496.
8. Feger T, Rupp N, Kuhn F, et al. Local and systemic eosinophil activation. *Ann Allergy Asthma Immunol* 1997;79: 221–225.
9. Cody D, Neel H, Gerreiro J, et al. Allergic fungal sinusitis: the Mayo Clinic experience. *Laryngoscope* 1994;104: 1074–1079.
10. Manning SC, Holman M. Further evidence for allergic pathophysiology in allergic fungal sinusitis. *Laryngoscope* 1998; 108:1485–1496.
11. Manning S, Vuitch F, Weinberg A, et al. Allergic aspergillosis: a newly recognized form of sinusitis in the pediatric population. *Laryngoscope* 1989;99:681–685.
12. Ponikau JU, Sherris DA, Kern EB, et al. The diagnosis and incidence of allergic fungal sinusitis. *Mayo Clin Proc* 1999; 74:877–884.
13. Corey JP. Allergic fungal sinusitis. *Otolaryngol Clin North Am* 1992;25:225–230.
14. Bent J, Kuhn F. Diagnosis of allergic fungal sinusitis. *Otolaryngol Head Neck Surg* 1994;111:580–588.
15. Deshpande RB, Shaukla A, Kirtane MV. Allergic fungal sinusitis: incidence and clinical and pathological features of seven cases. *J Assoc Physicians India* 1995;43:98–100.
16. Ferguson BJ, et al. Geographic distribution of AFS. *Otolaryngol Clin North Am* 2000;33:441–449.
17. Marple BF, Gibbs SR, Newcomer MT, Mabry RL. Allergic fungal sinusitis-induced visual loss. *Am J Rhinol* 1999;13: 191–195.
18. Manning S, Schaefer S, Close L, et al. Culture-positive allergic fungal sinusitis. *Arch Otolaryngol Head Neck Surg* 1991;117:174–178.
19. Marple BF, Mabry RL. Comprehensive management of allergic fungal sinusitis. *Am J Rhinol* 1998;12:263–268.
20. Marple BF. Allergic fungal sinusitis. *Curr Opin Otolaryngol* 1999;7:383–387.
21. Nussenbaum B, Marple BF, Schwade ND. Characteristics of bony erosion in allergic fungal sinusitis. *Otolaryngol Head Neck Surg* 2001;124:150–154.
22. Carter KD, Graham SM, Carpenter KM. Ophthalmologic manifestations of allergic fungal sinusitis. *Am J Ophthalmol* 1999;127:189–195.
23. Mukherjig SK, Figueroa R, Ginsberg LE, et al. Allergic fungal sinusitis: CT findings. *Radiology* 1998;207:417–422.
24. Zinreich SJ, Kennedy DW, Fullerton GD. Fungal sinusitis: diagnosis with CT and MR imaging. *Radiology* 1988;169: 439–444.
25. Som PM, Curtin HD. Chronic inflammatory sinonasal disease including fungal infections: the role of imaging. *Radiol Clin North Am* 1993;31:33–44.
26. Manning SC, Merkel M, Kreisel K, Vuitch F, Marple B. Computed tomographic and magnetic resonance diagnosis of allergic fungal sinusitis. *Laryngoscope* 1997;107: 170–176.
27. Schubert MS, Goetz DW. Evaluation and treatment of allergic fungal sinusitis. II: treatment and follow-up. *J Allergy Clin Immunol* 1998;102:395–402.
28. Manning S, Mabry R, Schaefer S, et al. Evidence of IgE-mediated hypersensitivity in allergic fungal sinusitis. *Laryngoscope* 1993;103:717–721.
29. Mabry R, Manning S. Radioallergosorbent microscreen and total immunoglobulin E in allergic fungal sinusitis. *Otolaryngol Head Neck Surg* 1995;113:721–723.
30. Mabry RL, Marple BF, Folker RJ, Mabry CS. Immunotherapy for allergic fungal sinusitis: three years' experience. *Otolaryngol Head Neck Surg* 1998;119:648–651.
31. Mabry RL, Marple BF, Mabry CS. Mold testing by RAST and skin test methods in patients with allergic fungal sinusitis. *Otolaryngol Head Neck Surg* 1999;121:252–254.
32. Chrzanowski RR, Rupp NT, Kuhn FA, Phillips AE, Dolen WK. Allergenic fungi in allergic fungal sinusitis. *Ann Allergy Asthma Immunol* 1997;79:431–435.
33. Schanadig VJ, Rassekh CH, Gourley WK. Allergic fungal sinusitis: a report of two cases with diagnosis by intraoperative aspiration cytology. *Acta Cytol* 1999;43:268–272.
34. Torres C, Rule out JY, el-Naggar AK, Sim SK, Weber RS, Ayala AG. Allergic fungal sinusitis: a clinicopathologic study of 16 cases. *Hum Pathol* 1996;27:793–799.
35. Millar J, Johnston, Lamb D. Allergic bronchopulmonary aspergillosis of the maxillary sinuses [Abstract]. *Thorax* 1981;36:710.
36. Allphin L, Strauss M, Abdul-Karim F. Allergic fungal sinusitis: problems in diagnosis and treatment. *Laryngoscope* 1991;10:815–820.
37. Loury MC, Schaefer SD. Allergic aspergillus sinusitis. *Arch Otolaryngol Head Neck Surg* 1993;119:1042–1043.
38. Berrettini S, Carabelli A, Papini M, Ciancia E, Sellari Franceschini allergic fungal sinusitis: is this rare disease an allergy or infection? *Acta Otorhinolaryngol Ital* 1996; 16:447–454.
39. deShazo RD, O'Brien M, Chapin K, et al. Criteria for the diagnosis of sinus mycetoma. *J Allergy Clin Immunol* 1997;99:4755–4785.
40. Ferguson BJ. *Immunotherapy and antifungal therapy in allergic fungal sinusitis.* Presented at the 1993 Annual Meeting of the American Academy of Otolaryngologic Allergy, Minneapolis, MN, September 1993:29.
41. McGuirt WF, Harrill JA. Paranasal sinus aspergillosis. *Laryngoscope* 1979;89:1563–1568.
42. Kupferberg SB, Bent JP, Kuhn FA. The prognosis of allergic fungal sinusitis. *Otolaryngol Head Neck Surg* 1997;117: 35–41.